June 15, 1958

Dear Joe:

This is a postscript to my last dictation, two items having been left out.

1. I would recommend your keeping a careful watch on the literature on specific tissue and organ-regulating substances. I have in mind especially 'hepatopoietin' and 'hematopoietin'. The former is in rather a confused state owing to contradictory reports by different investigators, and I don't know the latest on it: the work is mainly based on the very rapid regeneration that takes place in the liver after partial hepatectomy. Hematopoietin is probably somewhat better defined now (cf. for example a review by Root about 3 years ago in Physiol. Reviews.) There are a number of clinical conditions in which compounds with these activities would be most useful (aplastic anemias; cirrhosis?) and there would be the further hope of developing equally specific inhibitory analogues. (This raises the hope, by the way, that you have a library service that can be alerted to flag particular categories of reports in current literature.)

2. It may well be time to re-evaluate the possible application of bacteriophage therapy in the light of current knowledge. This did not work out too well thirty years ago, but in view of the great advances since then in technique of production and purification of phage, in the incidence and importance of resistant mutants, and in the mechanism of action of phage-killing, it is probably time for a new look.

As a test system, I would recommend the phage O-1 which attacks almost all smooth strains of Salmonella, and has been used as a diagnostic test for them. Resistant mutants do indeed occur, but most of them are simply rough (and therefore avirulent); the residue, if they prove to be a problem might be dealt with by other phages or antibiotics. I would consider it extremely important to have high-titered preparations of carefully purified bacteriophage for the purpose.

In fact, the intact phage might be just the first step, since most virulent phages act by means of a bactericidal protein at the tail tip, and this might be extracted and used in purified form. Probably the main disadvantage of phage therapy is the antigenicity of the phage antigens, so that host antibody would eventually neutralise the phage. Nevertheless, I would urge your careful consideration of this approach.

I can send you phage O-1 at any time you express your interest. It can be grown on any of a number of strains, including some of minimal or at least unknown pathogenicity for man.

Yours

Max